Universal definition of myocardial infarction: what must we know? What is next?

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In the beginning of the 20th century, the first reports of the clinical manifestations of myocardial infarction (MI) appeared, followed around a decade later by reports regarding the electrocardiographic (ECG) changes associated with MI (figure 1). From the middle of the 20th century, the application of assays for muscle enzymes for the diagnosis of MI became widespread, culminating in the WHO definition of MI based on clinical, ECG and cardiac enzyme criteria. Towards the end of the 20th century, the assays for cardiac troponins (I and T) became refined and were rapidly adopted by the cardiology community, allowing for more accurate diagnosis of MI. Accordingly, an American/European consensus document redefining MI was adopted for the first time, defining MI as clinical evidence of cardiac ischaemia and maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values for a reference control group) on at least one occasion during the first 24 hours after the index clinical event.[1] Since then, there have been three more iterations to this document, with the latest fourth universal definition of MI published in 2018 and adopted by cardiac societies around the globe, accounting for five different types of MI (table 1).[2] The principle that MI is defined by a clinical scenario of ischaemia and evidence of myocardial injury was loosely preserved in the different iterations. Several key caveats have arisen regarding the use of this latest definition.

MYOCARDIAL INJURY

Over the years, the sensitivity of troponin assays has dramatically increased, and accordingly, the 99th percentile has been lowered by almost 10-fold. Recent guidelines have highlighted the value of detecting values under the 99th percentile to rule-out or rule-in patients with suspected acute coronary syndromes.[3] Combination of assays for troponins and other peptides such as myosin-binding protein C may allow for even more rapid and accurate diagnose of minimal myocardial injury. These trials have relied on assays performed in a central laboratory. Point-of-care assays, which are becoming accurate enough to receive clinical certification, may have different thresholds altogether. On the other hand, the current definition of peri-procedural MI relies on threshold values several-fold greater than the 99th percentile, rendering the definition of myocardial injury elastic rather than a binary definition above or below a certain level. All in all, it seems across many studies that the greater the value of troponin, the worse the prognosis.

It is also important to bear in mind that some patients have chronically elevated circulating troponin levels, accounting for chronic myocardial injury. In these patients, it is more difficult to diagnose situations associated with acute cardiac injury, such as MI. There have been several proposals regarding how to diagnose acute-on-chronic injury based on absolute or relative increase in troponin levels, but these are quite arbitrary. Thus, the definition of MI is most accurate in a patient with a baseline value of troponin, which is considered 'normal'.

MYOCARDIAL ISCHAEMIA

In contrast to myocardial injury, there is no defined and measurable parameter for myocardial ischaemia. Clinicians can easily identify a patient with typical angina and ST-segment elevation as experiencing ischaemia, but the clinical and ECG manifestations may be much more subtle, making it very difficult to differentiate between mere myocardial injury and MI. This conundrum is often encountered by clinicians entertaining the diagnosis of type 2 MI, explaining the great variability in the reported incidence of this condition in the literature.

CLASSIFICATION OF MI

The different types of MI may be difficult for classification without coronary angiography or advanced coronary imaging, which are helpful but not mandatory for the diagnosis and classification of MI. For example, pathologies other than atherothromosis, such as spontaneous coronary dissection, may sometimes be appreciated only by using optical coherence tomography. Otherwise, the patient may be misclassified.

It is worth mentioning that several clinical scenarios, such as myocarditis and Takotsubo cardiomyopathy, may have clinical, ECG and biomarker features that closely mimic MI. It is often difficult to differentiate these scenarios from MI. Advanced cardiac imaging, using modalities such as cardiac magnetic resonance, may be crucial in making the right diagnosis. Otherwise, these patients may be erroneously classified as having MI. These modalities are recommended in the current definition of MI document but are understandably not mandatory.

Advanced coronary and cardiac imaging modalities are not widely available around the globe. Therefore, although the universal definition of MI aims to offer a global classification of ischaemic events, the classification of the different types of MI may be less accurate in underprivileged countries. This should be borne in mind when comparing the incidence of MI types between different countries.

CLINICAL SIGNIFICANCE OF MI

The clinical significance of the different types of MI has been the subject of intense controversy. Although it seems that spontaneous MI (type 1) portends worse outcomes than peri-procedural MI (types 4A and 5), in clinical trials these are often lumped together or given similar weight. This may severely skew the interpretation of the trials' results, especially given that the thresholds defining peri-procedural myocardial injury are arbitrary and several-fold greater than the 99th percentile, with some clinicians/researchers using threshold values that are 70-fold greater.

TREATMENT BASED ON TYPE OF MI

Current acute coronary syndrome guidelines by and large pertain to patients with type 1 MI because the clinical trials have primarily included these patients.[3] Only recently, randomised clinical trials to search for the optimal treatment of type 2 MI have been done.[4] Can we assume that what is good for a type 1 MI is good for a type 2 MI? Given the diverse aetiologies for type 2 MI, is the treatment nevertheless the same for the various subtypes? The optimal management of a patient after peri-procedural MI is also ill-defined. Some may argue that if we do not have specific guidelines as to how to treat these other types of MI, why should we differentially code them?

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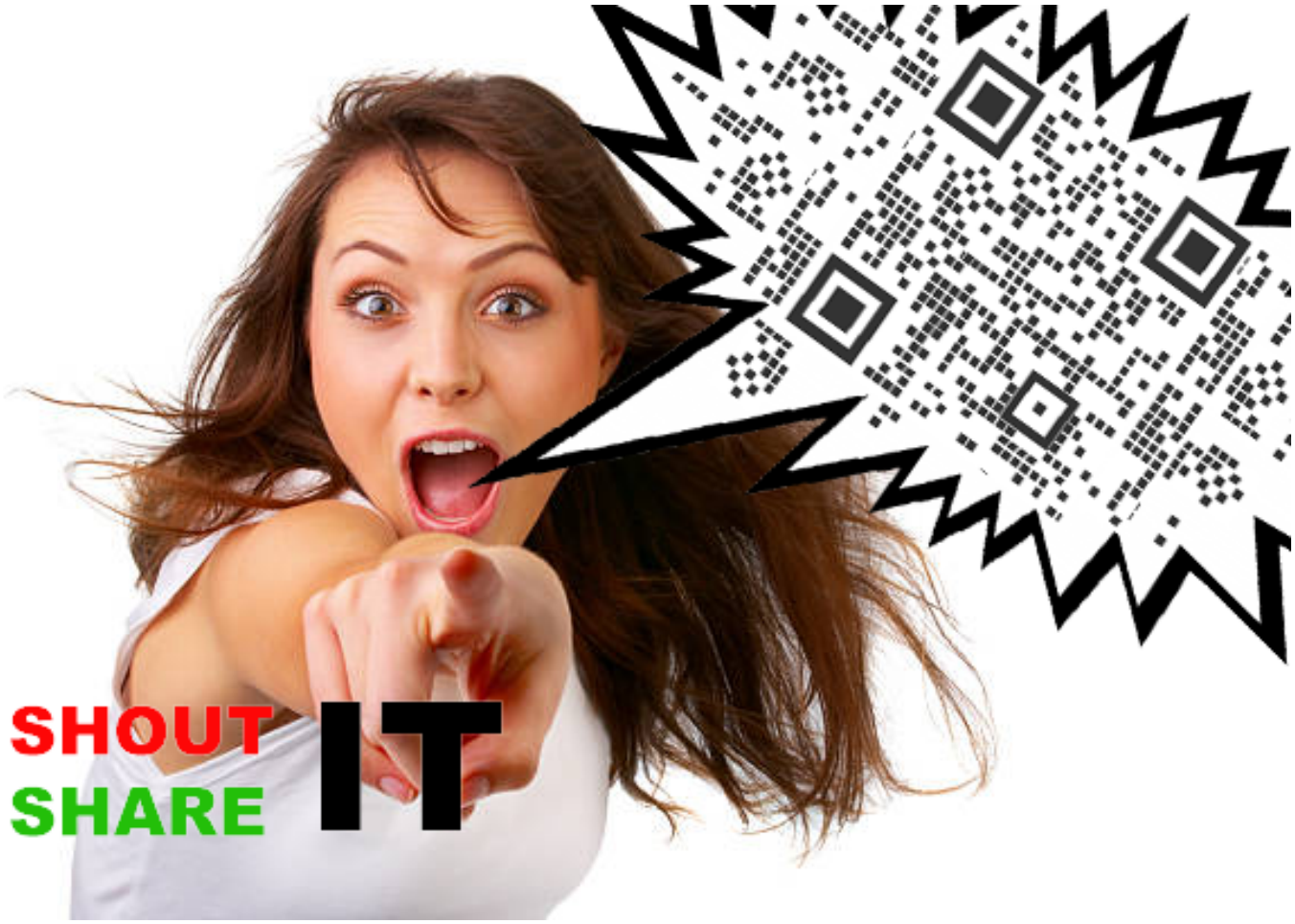
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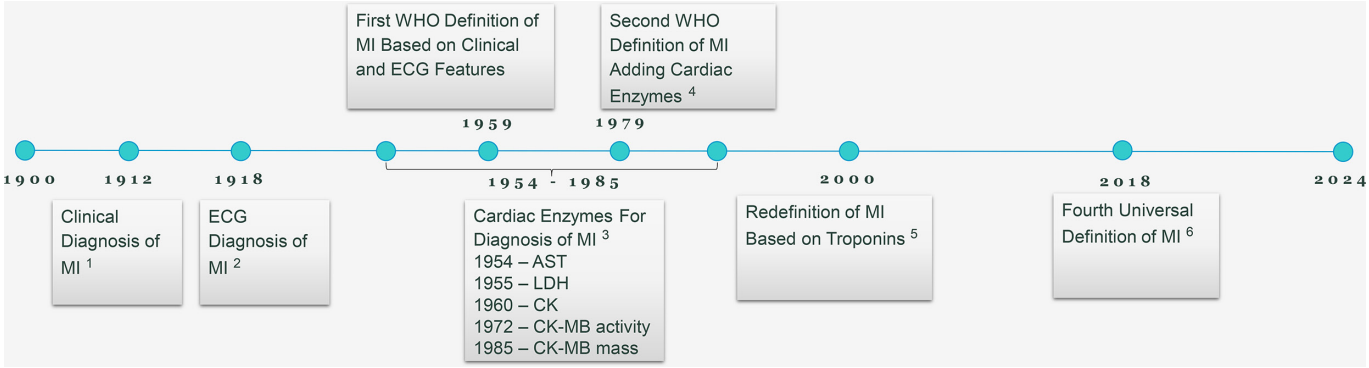

Figure 1 The evolution of the diagnosis of MI over the years. AST, aspartte transferase; CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; ECG, electrocardiographic; LDH, lactate dehydrogenase; MI, myocardial infarction.[1]*JAMA* 1912;59:2015–20. [2]*Arch Int Med* 1918;22:8–27. [3]*Ann Transl Med* 2016;4:194. [4]*Circulation* 1979;59:607–9. [5]*Eur Heart J* 2000;21:1502–13. [6]Eur Heart J 2019;40:237–69.

Table 1 Fourth universal definition of myocardial infarction (2018)—troponin (cTn) thresholds and caveats

Type	Biomarker thresholds	Caveats
1. Due to acute sequala of atherothrombotic coronary artery disease	Rise and/or fall of cTn values with ≥1 value >99th percentile	Rule in and rule out of MI based on hs-cTn values <99th percentile
2. Due to mismatch between myocardial oxygen supply and demand	Rise and/or fall of cTn values with ≥1 value >99th percentile	Broad definition that includes different mechanisms with overlap to the type 1 MI group. Values <99th percentile not yet validated.
3. Due to suspected acute myocardial ischaemic event resulted in patient death when cardiac biomarker evidence of MI is lacking	Biomarkers are not necessary for diagnosis	
4A. MI associated with percutaneous coronary intervention	Elevation of cTn values >5 times the 99th percentile if normal baseline values, or if elevated pre-procedure cTn and cTn levels are stable or falling, post-procedure cTn rise >20% to an absolute value >5 times the 99th percentile	Arbitrary. Difficulty in using these criteria in a patient in the context of rising cTn.
4B. Stent/scaffold thrombosis associated with percutaneous coronary intervention	Rise and/or fall of cTn values with ≥1 value >99th percentile	Difficulty in using these criteria in a patient in the context of rising cTn
4C. Re-stenosis associated with percutaneous coronary intervention	Rise and/or fall of cTn values with ≥1 value >99th percentile	
5. MI associated with coronary artery bypass grafting	>10 times the 99th percentile if normal baseline cTn values, or if elevated pre-procedure cTn and cTn levels are stable or falling, post-procedure cTn rise by >20% to an absolute value >10 times the 99th percentile	An arbitrary definition that is not commonly used

hs-cTn, high-sensitive cardiac troponin; MI, myocardial infarction.

GIVEN ALL THESE SHORTCOMING, WHY SHOULD WE USE THE CURRENT DEFINITION OF MI?

Definitions provide a basis for common understanding. Although the current universal definition is far from perfect, it does enable clinicians and researchers to describe scenarios using a common language. Like any language, these definitions are likely to evolve over time. Biomarkers to identify myocardial injury are likely to improve over time, enabling the identification of even minute necrosis of cardiac myocytes. This may increase the spectrum of MI from minimal myocardial necrosis to extensive myocardial damage. One may envision the introduction of a measurable biomarker to identify and measure cardiac ischaemia, a key and often elusive component of the current definition. Advanced coronary and cardiac imaging modalities, invasive and non-invasive, will likely become widely available, allowing for imaging of coronary anatomy, histology and physiology, and thus for better classification of the different types of MI. Cardiac imaging will likely enable better tissue characterisation, allowing for improved diagnosis of situations mimicking MI. Trials dedicated to investigate the optimal management for the different types and subtypes of MI, other than type 1, are expected, and these may enable for the first time-specific guidelines based on the type of MI. Despite these expected changes, the principle underlying the current definition of MI, namely, that MI is defined by cardiac injury attributed to cardiac ischaemia, will likely persist.

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